Therapeutic targeting of early erythroid progenitors

By

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Healthy bone marrow produces immature blood cells — called stem cells and progenitor cells — which normally develop into mature, fully functional red blood cells. The early erythroid progenitor, burst-forming unit erythroid (BFU-E), is the first erythroid lineage committed progenitor and possesses substantial capacity to undergo expansion. This unique property of BFU-E has shown immense therapeutic potential and yet its regulators and underlying mechanisms of its expansion are unclear. Here, I have uncovered multiple regulators of BFU-E expansion and its potential mechanisms. Genetic as well as pharmacological inhibition of cholinergic acetylcholine receptor muscarinic 4 (CHRM4) and carbonic anhydrase 13 (CAR13) stimulated BFU-E expansion and differentiation. Furthermore, CHRM4 and CAR13 inhibitors alleviated anemic symptoms by promoting BFU-E expansion and producing more erythrocytes in splicing factor mutant mouse models of myelodysplastic syndrome (MDS), where chronic anemia is the major phenotype. Moreover, knockout mouse models of Chrm4 and Car13 up-regulated BFU-E expansion during stress erythropoiesis. Mechanistically, CHRM4 inhibition upregulates cAMP/CREB signaling axis and thereby promotes upregulation of many genes responsible for BFU-E expansion. CAR13 inhibition causes assimilation of its substrate bicarbonate with ammonia to support high expansion state of BFU-E. Altogether, I have identified multiple druggable regulators of BFU-E expansion which can be utilized to treat variety of anemias.

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